

OCT 10 2000

NDA 19-668/S-014

Pfizer Inc.  
Attention: Mr. Robert Clark  
235 East 42nd Street  
New York, NY 100 17-5755

Dear Mr. Clark:

Please refer to your supplemental new drug application dated July 25, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardura (doxazosin mesylate) 1, 2, 4 and 8 mg Tablets.

This "Changes Being Effected" supplemental new drug application provides for final printed labeling revised as follows:

1. The CONTRAINDICATIONS section has been changed from:

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin.

to:

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin), doxazosin, or any of the inert ingredients.

2. Under WARNINGS/Priapism, the following phrase in the first sentence has been changed from:

such as doxazosin

to:

including doxazosin

3. The following paragraph has been added to the end of the ADVERSE REACTIONS section:

In post-marketing experience the following additional adverse reactions have been reported: *Autonomic Nervous System*: priapism; *Central nervous System*: hypoesthesia; *Endocrine System*: gynecomastia; *Gastrointestinal System*: vomiting; *General Body System*: allergic reaction; *Heart Rate/Rhythm*: bradycardia; *Hematopoietic*: leukopenia, thrombocytopenia; *Liver/Biliary System*: hepatitis, hepatitis cholestatic; *Respiratory System*: broncospasm aggravated; *Urinary System*: hematuria, micturition disorder, micturition frequency, nocturia.

4. Under the HOW SUPPLIED section, "CAUTION: Federal law prohibits dispensing without prescription," has been changed to, "Rx."

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your July 25, 2000 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely,

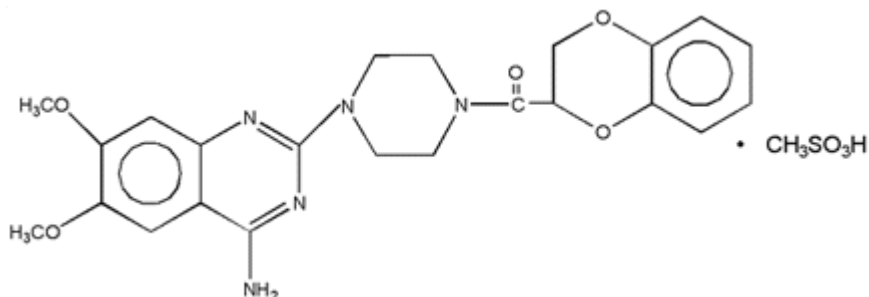
Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

70-4538-00-7

**CARDURA<sup>®</sup>**  
**(doxazosin mesylate)**  
**Tablets**

**DESCRIPTION**

CARDURA<sup>®</sup> (doxazosin mesylate) is a quinazoline compound that is a selective inhibitor of the  $\alpha_1$  subtype of alpha adrenergic receptors. The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is  $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$  and the molecular weight is 547.6. It has the following structure:



CARDURA<sup>®</sup> (doxazosin mesylate) is freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8% at 25°C), and very slightly soluble in acetone and methylene chloride. CARDURA<sup>®</sup> is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) of doxazosin as the free base.

The inactive ingredients for all tablets are: microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate and sodium lauryl sulfate. The 2 mg tablet contains D & C yellow 10 and FD & C yellow 6; the 4 mg tablet contains FD & C yellow 6; the 8 mg tablet contains FD & C blue 10 and D & C yellow 10.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

**A. Benign Prostatic Hyperplasia (BPH)**

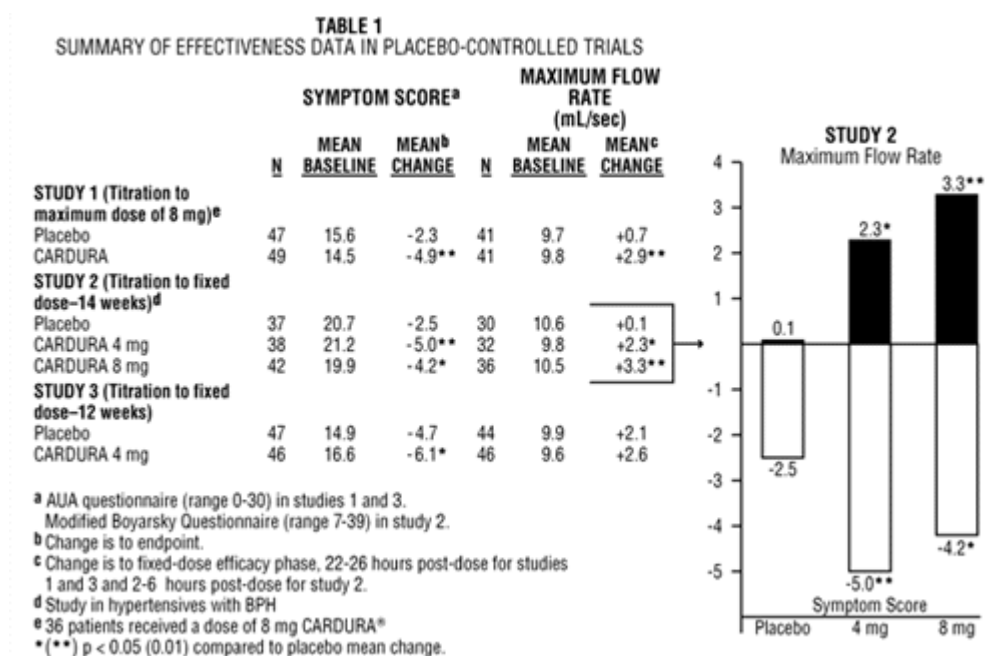
Benign prostatic hyperplasia (BPH) is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retention and renal damage. A static and a dynamic component contribute to the symptoms and reduced urinary flow rate associated with BPH. The static component is related to an increase in prostate size

caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the  $\alpha_1$  adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockade of the  $\alpha_1$  receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In the human prostate, CARDURA® antagonizes phenylephrine ( $\alpha_1$  agonist)-induced contractions, *in vitro*, and binds with high affinity to the  $\alpha_{1C}$  adrenoceptor. The receptor subtype is thought to be the predominant functional type in the prostate. CARDURA® acts within 1-2 weeks to decrease the severity of BPH symptoms and improve urinary flow rate. Since  $\alpha_1$  adrenoceptors are of low density in the urinary bladder (apart from the bladder neck), CARDURA® should maintain bladder contractility.

The efficacy of CARDURA® was evaluated extensively in over 900 patients with BPH in double-blind, placebo-controlled trials. CARDURA® treatment was superior to placebo in improving patient symptoms and urinary flow rate. Significant relief with CARDURA® was seen as early as one week into the treatment regimen, with CARDURA® treated patients (N=173) showing a significant ( $p < 0.01$ ) increase in maximum flow rate of 0.8 mL/sec compared to a decrease of 0.5 mL/sec in the placebo group (N=41). In long-term studies improvement was maintained for up to 2 years of treatment. In 66-71% of patients, improvements above baseline were seen in both symptoms and maximum urinary flow rate.

In three placebo-controlled studies of 14-16 weeks duration obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) of BPH were evaluated at each visit by patient-assessed symptom questionnaires. The bothersomeness of symptoms was measured with a modified Boyarsky questionnaire. Symptom severity/frequency was assessed using a modified Boyarsky questionnaire or an AUA-based questionnaire. Uroflowmetric evaluations were performed at times of peak (2-6 hours post-dose) and/or trough (24 hours post-dose) plasma concentrations of CARDURA®.

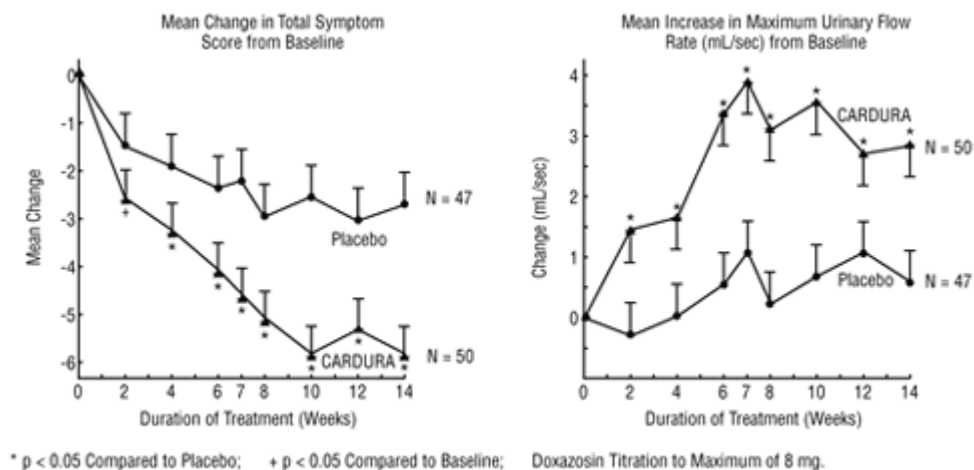
The results from the three placebo-controlled studies (N=609) showing significant efficacy with 4 mg and 8 mg doxazosin are summarized in Table 1. In all three studies, CARDURA® resulted in statistically significant relief of obstructive and irritative symptoms compared to placebo. Statistically significant improvements of 2.3-3.3 mL/sec in maximum flow rate were seen with CARDURA® in Studies 1 and 2, compared to 0.1-0.7 mL/sec with placebo.



In one fixed dose study (Study 2) CARDURA® (doxazosin mesylate) therapy (4-8 mg, once daily) resulted in a

significant and sustained improvement in maximum urinary flow rate of 2.3-3.3 mL/sec (Table 1) compared to placebo (0.1 mL/sec). In this study, the only study in which weekly evaluations were made, significant improvement with CARDURA® vs. placebo was seen after one week. The proportion of patients who responded with a maximum flow rate improvement of  $\geq 3$  mL/sec was significantly larger with CARDURA® (34-42%) than placebo (13-17%). A significantly greater improvement was also seen in average flow rate with CARDURA® (1.6 mL/sec) than with placebo (0.2 mL/sec). The onset and time course of symptom relief and increased urinary flow from Study 1 are illustrated in Figure 1.

**Figure 1 - Study 1**



In BPH patients (N=450) treated for up to 2 years in open-label studies, CARDURA® therapy resulted in significant improvement above baseline in urinary flow rates and BPH symptoms. The significant effects of CARDURA® were maintained over the entire treatment period.

Although blockade of  $\alpha_1$  adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, CARDURA® treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (Table 2). The proportion of normotensive patients with a sitting systolic blood pressure less than 90 mmHg and/or diastolic blood pressure less than 60 mmHg at any time during treatment with CARDURA® 1-8 mg once daily was 6.7% with doxazosin and not significantly different (statistically) from that with placebo (5%).

**TABLE 2**  
Mean Changes in Blood Pressure from Baseline to the Mean of the Final Efficacy Phase in Normotensives (Diastolic BP < 90 mmHg) in Two Double-blind, Placebo-controlled U.S. Studies with CARDURA® 1-8 mg once daily.

	PLACEBO (N=85)		CARDURA® (N=183)	
<u>Sitting BP (mmHg)</u>	<u>Baseline</u>	<u>Change</u>	<u>Baseline</u>	<u>Change</u>
Systolic	128.4	-1.4	128.8	-4.9*
Diastolic	79.2	-1.2	79.6	-2.4*
<u>Standing BP (mmHg)</u>	<u>Baseline</u>	<u>Change</u>	<u>Baseline</u>	<u>Change</u>
Systolic	128.5	-0.6	128.5	-5.3*
Diastolic	80.5	-0.7	80.4	-2.6*

\*p ≤0.05 compared to placebo

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## **B. Hypertension**

The mechanism of action of CARDURA® (doxazosin mesylate) is selective blockade of the  $\alpha_1$  (postjunctional) subtype of adrenergic receptors. Studies in normal human subjects have shown that doxazosin competitively antagonized the pressor effects of phenylephrine (an  $\alpha_1$  agonist) and the systolic pressor effect of norepinephrine. Doxazosin and prazosin have similar abilities to antagonize phenylephrine. The antihypertensive effect of CARDURA® results from a decrease in systemic vascular resistance. The parent compound doxazosin is primarily responsible for the antihypertensive activity. The low plasma concentrations of known active and inactive metabolites of doxazosin (2-piperazinyl, 6'- and 7'-hydroxy and 6- and 7-O-desmethyl compounds) compared to parent drug indicate that the contribution of even the most potent compound (6'-hydroxy) to the antihypertensive effect of doxazosin in man is probably small. The 6'- and 7'-hydroxy metabolites have demonstrated antioxidant properties at concentrations of 5  $\mu\text{M}$ , *in vitro*.

Administration of CARDURA® results in a reduction in systemic vascular resistance. In patients with hypertension there is little change in cardiac output. Maximum reductions in blood pressure usually occur 2-6 hours after dosing and are associated with a small increase in standing heart rate. Like other  $\alpha_1$ -adrenergic blocking agents, doxazosin has a greater effect on blood pressure and heart rate in the standing position.

In a pooled analysis of placebo-controlled hypertension studies with about 300 hypertensive patients per treatment group, doxazosin, at doses of 1-16 mg given once daily, lowered blood pressure at 24 hours by about 10/8 mmHg compared to placebo in the standing position and about 9/5 mmHg in the supine position. Peak blood pressure effects (1-6 hours) were larger by about 50-75% (i.e., trough values were about 55-70% of peak effect), with the larger peak-trough differences seen in systolic pressures. There was no apparent difference in the blood pressure response of Caucasians and blacks or of patients above and below age 65. In these predominantly normocholesterolemic patients doxazosin produced small reductions in total serum cholesterol (2-3%), LDL cholesterol (4%), and a similarly small increase in HDL/total cholesterol ratio (4%). The clinical significance of these findings is uncertain. In the same patient population, patients receiving CARDURA® gained a mean of 0.6 kg compared to a mean loss of 0.1 kg for placebo patients.

### **Pharmacokinetics**

After oral administration of therapeutic doses, peak plasma levels of CARDURA® (doxazosin mesylate) occur at about 2-3 hours. Bioavailability is approximately 65%, reflecting first pass metabolism of doxazosin by the liver. The effect of food on the pharmacokinetics of CARDURA® was examined in a crossover study with twelve hypertensive subjects. Reductions of 18% in mean maximum plasma concentration and 12% in the area under the concentration-time curve occurred when CARDURA® was administered with food. Neither of these differences was statistically or clinically significant.

CARDURA® is extensively metabolized in the liver, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites have not been characterized. In a study of two subjects administered radiolabelled doxazosin 2 mg orally and 1 mg intravenously on two separate occasions, approximately 63% of the dose was eliminated in the feces and 9% of the dose was found in the urine. On average only 4.8% of the dose was excreted as unchanged drug in the feces and only a trace of the total radioactivity in the urine was attributed to unchanged drug. At the plasma concentrations achieved by therapeutic doses approximately 98% of the circulating drug is bound to plasma proteins.

Plasma elimination of doxazosin is biphasic, with a terminal elimination half-life of about 22 hours. Steady-state studies in hypertensive patients given doxazosin doses of 2-16 mg once daily showed linear kinetics and dose proportionality. In two studies, following the administration of 2 mg orally once daily, the mean accumulation ratios (steady-state AUC vs. first dose AUC) were 1.2 and 1.7. Enterohepatic recycling is suggested by secondary peaking of plasma doxazosin concentrations.

In a crossover study in 24 normotensive subjects, the pharmacokinetics and safety of doxazosin were shown to be similar with morning and evening dosing regimens. The area under the curve after morning dosing was, however, 11% less than that after evening dosing and the time to peak concentration after evening dosing occurred

significantly later than that after morning dosing (5.6 hr vs. 3.5 hr).

The pharmacokinetics of CARDURA® (doxazosin mesylate) in young (<65 years) and elderly (≥65 years) subjects were similar for plasma half-life values and oral clearance. Pharmacokinetic studies in elderly patients and patients with renal impairment have shown no significant alterations compared to younger patients with normal renal function. Administration of a single 2 mg dose to patients with cirrhosis (Child-Pugh Class A) showed a 40% increase in exposure to doxazosin. There are only limited data on the effects of drugs known to influence the hepatic metabolism of doxazosin [e.g., cimetidine (see PRECAUTIONS)]. As with any drug wholly metabolized by the liver, use of CARDURA® in patients with altered liver function should be undertaken with caution.

In two placebo-controlled studies, of normotensive and hypertensive BPH patients, in which doxazosin was administered in the morning and the titration interval was two weeks and one week, respectively, trough plasma concentrations of CARDURA® were similar in the two populations. Linear kinetics and dose proportionality were observed.

## INDICATIONS AND USAGE

**A. Benign Prostatic Hyperplasia (BPH).** CARDURA® is indicated for the treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH: obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning). CARDURA® may be used in all BPH patients whether hypertensive or normotensive. In patients with hypertension and BPH, both conditions were effectively treated with CARDURA® monotherapy. CARDURA® provides rapid improvement in symptoms and urinary flow rate in 66-71% of patients. Sustained improvements with CARDURA® were seen in patients treated for up to 14 weeks in double-blind studies and up to 2 years in open-label studies.

**B. Hypertension.** CARDURA® (doxazosin mesylate) is also indicated for the treatment of hypertension. CARDURA® may be used alone or in combination with diuretics, beta-adrenergic blocking agents, calcium channel blockers or angiotensin-converting enzyme inhibitors.

## CONTRAINDICATIONS

CARDURA® is contraindicated in patients with a known sensitivity to quinazolines (e.g., prazosin, terazosin), doxazosin, or any of the inert ingredients.

## WARNINGS

**Syncope and "First-dose" Effect:** Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with evaluations and increases in dose every two weeks to the recommended dose. Additional antihypertensive agents should be added with caution.

**Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night.**

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without

experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study, 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials in hypertension involving over 1500 hypertensive patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

In placebo-controlled, clinical trials in BPH, 3 out of 665 patients (0.5%) taking doxazosin reported syncope. Two of the patients were taking 1 mg doxazosin, while one patient was taking 2 mg doxazosin when syncope occurred. In the open-label, long-term extension follow-up of approximately 450 BPH patients, there were 3 reports of syncope (0.7%). One patient was taking 2 mg, one patient was taking 8 mg and one patient was taking 12 mg when syncope occurred. In a clinical pharmacology study, one subject receiving 2 mg experienced syncope.

**If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.**

**Priapism:** Rarely (probably less frequently than once in every several thousand patients),  $\alpha_1$  antagonists, including doxazosin, have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see **PRECAUTIONS: Information for Patients**).

## PRECAUTIONS

### General:

**Prostate Cancer:** Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders frequently co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with CARDURA®.

**Orthostatic Hypotension:** While syncope is the most severe orthostatic effect of CARDURA®, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo can occur, especially at initiation of therapy or at the time of dose increases.

#### a) Hypertension

These symptoms were common in clinical trials in hypertension, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo-controlled titration trials in hypertension, orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

#### b) Benign Prostatic Hyperplasia

In placebo-controlled trials in BPH, the incidence of orthostatic hypotension with doxazosin was 0.3% and did not increase with increasing dosage (to 8 mg/day). The incidence of discontinuations due to hypotensive or orthostatic symptoms was 3.3% with doxazosin and 1% with placebo. The titration interval in these studies was one to two weeks.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution. As  $\alpha_1$  antagonists can cause orthostatic effects, it is important to evaluate standing blood pressure two minutes after standing and patients should be advised to exercise care when arising from a supine or sitting position.



If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA® (doxazosin mesylate).

**Information for Patients (See patient package insert):** Patients should be made aware of the possibility of syncope and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with CARDURA® (doxazosin mesylate) or any selective  $\alpha_1$  adrenoceptor antagonist, requiring caution in people who must drive or operate heavy machinery.

Patients should be advised about the possibility of priapism as a result of treatment with  $\alpha_1$  antagonists.

Patients should know that this adverse event is very rare. If they experience priapism, it should be brought to immediate medical attention for if not treated promptly it can lead to permanent erectile dysfunction (impotence).

**Drug/Laboratory Test Interactions:** CARDURA® does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years. Both doxazosin, an  $\alpha_1$  inhibitor, and finasteride, a 5- $\alpha$  reductase inhibitor, are highly protein bound and hepatically metabolized. There is no definitive controlled clinical experience on the concomitant use of  $\alpha_1$  inhibitors and 5- $\alpha$  reductase inhibitors at this time.

**Impaired Liver Function:** CARDURA® should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY).

**Leukopenia/Neutropenia:** Analysis of hematologic data from hypertensive patients receiving CARDURA® in controlled hypertension clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0%, respectively, compared to placebo, a phenomenon seen with other  $\alpha$  blocking drugs. In BPH patients the incidence of clinically significant WBC abnormalities was 0.4% (2/459) with CARDURA® and 0% (0/147) with placebo, with no statistically significant difference between the two treatment groups. A search through a data base of 2400 hypertensive patients and 665 BPH patients revealed 4 hypertensives in which drug-related neutropenia could not be ruled out and one BPH patient in which drug related leukopenia could not be ruled out. Two hypertensives had a single low value on the last day of treatment. Two hypertensives had stable, non-progressive neutrophil counts in the  $1000/\text{mm}^3$  range over periods of 20 and 40 weeks. One BPH patient had a decrease from a WBC count of  $4800/\text{mm}^3$  to  $2700/\text{mm}^3$  at the end of the study; there was no evidence of clinical impairment. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA®. No patients became symptomatic as a result of the low WBC or neutrophil counts.

**Drug Interactions:** Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA® has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA® has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta-blocking agents, and nonsteroidal anti-inflammatory drugs. In a placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin ( $p=0.006$ ), and a slight but not statistically significant increase in mean  $C_{\text{max}}$  and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

In clinical trials, CARDURA® tablets have been administered to patients on a variety of concomitant medications; while no formal interaction studies have been conducted, no interactions were observed. CARDURA® tablets have been used with the following drugs or drug classes: 1) analgesic/anti-inflammatory (e.g., acetaminophen, aspirin, codeine and codeine combinations, ibuprofen, indomethacin); 2) antibiotics (e.g., erythromycin, trimethoprim and sulfamethoxazole, amoxicillin); 3) antihistamines (e.g., chlorpheniramine); 4) cardiovascular agents (e.g., atenolol, hydrochlorothiazide, propranolol); 5) corticosteroids; 6) gastrointestinal agents (e.g., antacids); 7)

hypoglycemics and endocrine drugs; 8) sedatives and tranquilizers (e.g., diazepam); 9) cold and flu remedies.

**Cardiac Toxicity in Animals:** An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (AUC exposure in rats 8 times the human AUC exposure with a 12 mg/day therapeutic dose). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months (exposure 8 times human AUC exposure in rats and somewhat equivalent to human  $C_{max}$  exposure in mice). No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs at maximum doses of 20 mg/kg/day [maximum plasma concentrations ( $C_{max}$ ) in dogs 14 times the  $C_{max}$  exposure in humans receiving a 12 mg/day therapeutic dose] and in Wistar rats at doses of 100 mg/kg/day ( $C_{max}$  exposures 15 times human  $C_{max}$  exposure with a 12 mg/day therapeutic dose). There is no evidence that similar lesions occur in humans.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated doses of 40 mg/kg/day in rats and 120 mg/kg/day in mice revealed no evidence of carcinogenic potential. The highest doses evaluated in the rat and mouse studies are associated with AUCs (a measure of systemic exposure) that are 8 times and 4 times, respectively, the human AUC at a dose of 16 mg/day.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 4 times the AUC exposures obtained with a 12 mg/day human dose. This effect was reversible within two weeks of drug withdrawal. There have been no reports of any effects of doxazosin on male fertility in humans.

**Pregnancy: Teratogenic Effects, Pregnancy Category C.** Studies in pregnant rabbits and rats at daily oral doses of up to 41 and 20 mg/kg, respectively (plasma drug concentrations 10 and 4 times human  $C_{max}$  and AUC exposures with a 12 mg/day therapeutic dose), have revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA® should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

**Nonteratogenic Effects:** In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin (8 times human AUC exposure with a 12 mg/day therapeutic dose) was delayed as evidenced by slower body weight gain and slightly later appearance of anatomical features and reflexes.

**Nursing Mothers:** Studies in lactating rats given a single oral dose of 1 mg/kg of [2-<sup>14</sup>C]-CARDURA® indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA® is administered to a nursing mother.

**Pediatric Use:** The safety and effectiveness of CARDURA® as an antihypertensive agent have not been established in children.

**Use in Elderly:** The safety and effectiveness profile of CARDURA® in BPH was similar in the elderly (age ≥65 years) and younger (age <65 years) patients.

## ADVERSE REACTIONS

### A. Benign Prostatic Hyperplasia

The incidence of adverse events has been ascertained from worldwide clinical trials in 965 BPH patients. The incidence rates presented below (Table 3) are based on combined data from seven placebo-controlled trials involving once daily administration of CARDURA® (doxazosin mesylate) in doses of 1-16 mg in hypertensives and 0.5-8 mg in normotensives. The adverse events when the incidence in the CARDURA® group was at least 1% are summarized in Table 3. No significant difference in the incidence of adverse events compared to placebo was seen except for dizziness, fatigue, hypotension, edema and dyspnea. Dizziness and dyspnea appeared to be dose-related.

**TABLE 3**  
**Adverse Reactions During Placebo-Controlled Studies**  
**Benign Prostatic Hyperplasia**

Body System	CARDURA® (N=665)	PLACEBO (N=300)
<b>BODY AS A WHOLE</b>		
Back pain	1.8%	2.0%
Chest pain	1.2%	0.7%
Fatigue	8.0%*	1.7%
Headache	9.9%	9.0%
Influenza-like symptoms	1.1%	1.0%
Pain	2.0%	1.0%
<b>CARDIOVASCULAR SYSTEM</b>		
Hypotension	1.7%*	0.0%
Palpitation	1.2%	0.3%
<b>DIGESTIVE SYSTEM</b>		
Abdominal Pain	2.4%	2.0%
Diarrhea	2.3%	2.0%
Dyspepsia	1.7%	1.7%
Nausea	1.5%	0.7%
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>		
Edema	2.7%*	0.7%
<b>NERVOUS SYSTEM</b>		
Dizziness	15.6%*	9.0%
Mouth Dry	1.4%	0.3%
Somnolence	3.0%	1.0%
<b>RESPIRATORY SYSTEM</b>		
Dyspnea	2.6%*	0.3%
Respiratory Disorder	1.1%	0.7%
<b>SPECIAL SENSES</b>		
Vision Abnormal	1.4%	0.7%
<b>UROGENITAL SYSTEM</b>		
Impotence	1.1%	1.0%
Urinary Tract Infection	1.4%	2.3%
<b>SKIN &amp; APPENDAGES</b>		
Sweating Increased	1.1%	1.0%
<b>PSYCHIATRIC DISORDERS</b>		
Anxiety	1.1%	0.3%
Insomnia	1.2%	0.3%

\*p ≤0.05 for treatment differences ·Includes vertigo

In these placebo-controlled studies of 665 CARDURA® patients, treated for a mean of 85 days, additional adverse reactions have been reported. These are less than 1% and not distinguishable from those that occurred in the placebo group. Adverse reactions with an incidence of less than 1% but of clinical interest are (CARDURA® vs. placebo): *Cardiovascular System*: angina pectoris (0.6% vs. 0.7%), postural hypotension (0.3% vs. 0.3%), syncope (0.5% vs. 0.0%), tachycardia (0.9% vs. 0.0%); *Urogenital System*: dysuria (0.5% vs. 1.3%), and

*Psychiatric Disorders:* libido decreased (0.8% vs. 0.3%). The safety profile in patients treated for up to three years was similar to that in the placebo-controlled studies.

The majority of adverse experiences with CARDURA® were mild.

## **B. Hypertension**

CARDURA® has been administered to approximately 4000 hypertensive patients, of whom 1679 were included in the hypertension clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled hypertension clinical trials directly comparing CARDURA® to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related. The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 4 summarizes those adverse experiences (possibly/probably related) reported for patients in these hypertension studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

**TABLE 4**  
**Adverse Reactions During Placebo-Controlled Studies**

	<b>HYPERTENSION</b>	
	<b>DOXAZOSIN</b> (N=339)	<b>PLACEBO</b> (N=336)
<b>CARDIOVASCULAR SYSTEM</b>		
Dizziness	19%	9%
Vertigo	2%	1%
Postural Hypotension	0.3%	0%
Edema	4%	3%
Palpitation	2%	3%
Arrhythmia	1%	0%
Hypotension	1%	0%
Tachycardia	0.3%	1%
Peripheral Ischemia	0.3%	0%
<b>SKIN &amp; APPENDAGES</b>		
Rash	1%	1%
Pruritus	1%	1%
<b>MUSCULOSKELETAL SYSTEM</b>		
Arthralgia/Arthritis	1%	0%
Muscle Weakness	1%	0%
Myalgia	1%	0%
<b>CENTRAL &amp; PERIPHERAL N.S.</b>		
Headache	14%	16%
Paresthesia	1%	1%
Kinetic Disorders	1%	0%
Ataxia	1%	0%
Hypertonia	1%	0%
Muscle Cramps	1%	0%
<b>AUTONOMIC</b>		
Mouth Dry	2%	2%
Flushing	1%	0%
<b>SPECIAL SENSES</b>		
Vision Abnormal	2%	1%
Conjunctivitis/Eye Pain	1%	1%
Tinnitus	1%	0.3%

**PSYCHIATRIC**

Somnolence	5%	1%
Nervousness	2%	2%
Depression	1%	1%
Insomnia	1%	1%
Sexual Dysfunction	2%	1%

**GASTROINTESTINAL**

Nausea	3%	4%
Diarrhea	2%	3%
Constipation	1%	1%
Dyspepsia	1%	1%
Flatulence	1%	1%
Abdominal Pain	0%	2%
Vomiting	0%	1%

**RESPIRATORY**

Rhinitis	3%	1%
Dyspnea	1%	1%
Epistaxis	1%	0%

**URINARY**

Polyuria	2%	0%
Urinary Incontinence	1%	0%
Micturition Frequency	0%	2%

**GENERAL**

Fatigue/Malaise	12%	6%
Chest Pain	2%	2%
Asthenia	1%	1%
Face Edema	1%	0%
Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA® has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA® has been associated with decreases in white blood cell counts (see PRECAUTIONS).

In post-marketing experience the following additional adverse reactions have been reported: *Autonomic Nervous System:* priapism; *Central Nervous System:* hypoesthesia; *Endocrine System:* gynecomastia; *Gastrointestinal System:* vomiting; *General Body System:* allergic reaction; *Heart Rate/Rhythm:* bradycardia; *Hematopoietic:* leukopenia, thrombocytopenia; *Liver/Biliary System:* hepatitis, hepatitis cholestatic; *Respiratory System:* bronchospasm aggravated; *Urinary System:* hematuria, micturition disorder, micturition frequency, nocturia.

**OVERDOSAGE**

Experience with CARDURA® overdosage is limited. Two adolescents who each intentionally ingested 40 mg CARDURA® with diclofenac or paracetamol, were treated with gastric lavage with activated charcoal and made

full recoveries. A two-year-old child who accidentally ingested 4 mg CARDURA® was treated with gastric lavage and remained normotensive during the five-hour emergency room observation period. A six-month-old child accidentally received a crushed 1 mg tablet of CARDURA® and was reported to have been drowsy. A 32-year-old female with chronic renal failure, epilepsy and depression intentionally ingested 60 mg CARDURA® (blood level 0.9 µg/mL; normal values in hypertensives = 0.02 µg/mL); death was attributed to a grand mal seizure resulting from hypotension. A 39-year-old female who ingested 70 mg CARDURA®, alcohol and Dalmane® (flurazepam) developed hypotension which responded to fluid therapy.

The oral LD<sub>50</sub> of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

## DOSAGE AND ADMINISTRATION

**DOSAGE MUST BE INDIVIDUALIZED.** The initial dosage of CARDURA® in patients with hypertension and/or BPH is 1 mg given once daily in the a.m. or p.m. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA®. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. If CARDURA® administration is discontinued for several days, therapy should be restarted using the initial dosing regimen.

**A. BENIGN PROSTATIC HYPERPLASIA 1-8 mg once daily.** The initial dosage of CARDURA® is 1 mg, given once daily in the a.m. or p.m. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily, the maximum recommended dose for BPH. The recommended titration interval is 1-2 weeks. Blood pressure should be evaluated routinely in these patients.

**B. HYPERTENSION 1-16 mg once daily.** The initial dosage of CARDURA® is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours post-dose and 24 hours post-dose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo and postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

## HOW SUPPLIED

CARDURA® (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS (doxazosin mesylate) are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100:	1 mg (NDC 0049-2750-66)
	2 mg (NDC 0049-2760-66)
	4 mg (NDC 0049-2770-66)
	8 mg (NDC 0049-2780-66)

Unit Dose Packages of 100:	1 mg (NDC 0049-2750-41)
	2 mg (NDC 0049-2760-41)
	4 mg (NDC 0049-2770-41)
	8 mg (NDC 0049-2780-41)

Recommended Storage: Store below 86°F (30°C).

**RX only**

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**Roerig**

Division of Pfizer Inc, NY, NY 10017

70-4538-00-7

Printed in U.S.A.  
Revised June 2000